Transdermal and Transdermal-like Delivery System Opportunities

a report by
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Introduction

Over the past 10 years or so, there have been over 7,000 transdermal-related presentations at the annual meetings of the Controlled Release Society (CRS) and American Association of Pharmaceutical Scientists. The CRS Annual International Symposia in 2004 has 100 papers related to transdermal and transdermal-like ('patch-like' technology).

Even though scientists and engineers continue to publish transdermal-related scientific papers in great numbers, it is intriguing to find such continued interest when only 10 or so new drugs utilising transdermal technology have been introduced over these past 20 years (see *Table 1*). While several companies may have developed compounds using different transdermal delivery systems (TDS) such as nitroglycerin, estradiol and nicotine, new transdermals incorporating a new compound seem to enter the marketplace just about every other year. It has only been recently that transdermal products themselves have reached their patent expiry date in the US, and generic versions are now lining up for launch. Fentanyl, estradiol, clonidine and nitroglycerin are drugs that have a sizable transdermal market.

This article provides a perspective on the history of transdermal and patch-like platforms, their current status and predictions on their future in the US.

Patch-like products refer to those products that are applied to the skin or mucosa and may consist of a flat film-like structure by itself (similar to TDS) or integrated as part of the product.

Recent Past

Transdermal drug delivery systems were first introduced over 20 years ago. The technology generated tremendous excitement and interest among the major pharmaceutical companies in the 1980s and 1990s. The advantages of avoidance of first-pass liver metabolism, avoidance of exposure to chemical and biological conditions of the gastrointestinal tract, reduction or avoidance of adverse events, improved patient compliance and the ability to provide controlled delivery of drugs with short half-lives and/or narrow therapeutic windows were all attractive features to the the pharmaceutical industry.

Excitement dwindled to disappointment, however, when the limitations of the existing transdermal technology became evident and the numbers of drug candidates were limited to nitroglycerin, scopolamine, clonidine, oestrogen, testosterone, nicotine and fentanyl.[1] Factors limiting the success of transdermal technology included local skin irritation associated with certain drugs and formulation, limitation on the dose of drug that could be delivered transdermally, a lag time associated with the delivery of the drug across the skin, resulting in a delay in onset of action, variation of absorption rate based on site of application, skin type and patient age and variation in adhesive effectiveness across skin types. These limitations, in addition to the rise in other non-oral drug delivery systems such as pulmonary delivery systems, caused interest in transdermal technology to decline. Without the interest of big pharma and the funding partnerships that they provided, few transdermal drug delivery companies could sustain themselves without a large pipeline leading products to the marketplace.

By the mid-to-late 1990s, the trend of TDS companies merging into larger organisations (for example Johnson & Johnson acquiring ALZA and a part of Cygnus, Watson and Theratech and Elan and Sano), combined with the increasing number of mega-pharmaceutical mergers, resulted in fewer companies wanting to develop transdermal products. Acceptance of transdermal technology by larger pharmaceutical companies became more conservative and development efforts remained focused on oral drug delivery. In 2001, only 15% of research and development budgets of major pharmaceutical companies were spent on projects

1. *IMS.*

Table 1: US Sales of Select Prescription Transdermal Products

Drug	Examples of Brand Names	Annual Sales (US$) MAT 9/00	Annual Sales (US$) MAT 9/01	Annual Sales (US$) MAT 9/02
Fentanyl	Duragesic	1.15b	1.29b	1.59b
Estradiol	Climara, Vivelle-Dot, CombiPatch	260m	253m	279m
Clonidine	Catapres TTS	133m	147m	168m
Nitroglycerin	Nitro-Dur, Deponit	209m	182m	159m
Nicotine	Nicoderm CQ, Nicotrol	88m	72m	73m
Testosterone	Testoderm TTS	43m	44m	50m
Ethinylestradiol and Norelgestromin	Ortho Evra			19m
Scopolamine	Transderm-Scop	12m	14m	17m
Lidocaine	Lidoderm		27m	60m
Oxybutynin	Awaiting FDA approval			
Methylphenidate	Awaiting FDA approval			

Source: IMS

*Table 2: Over-the-Counter Patch Products Currently Marketed**

NeoSkin Aromatherapy Cucumber Pads	HerbalPad Echinacea and Golden Seal
NeoSkin Pre-formed Moisture Mask	HerbalPad Ginkgo Biloba
NeoSkin Hydrating Wrinkle Patch	HerbalPad Glucosamine and Chondroitin
NeoSkin Pre-formed Moisture Mask	HerbalPad St. John s Wort
DuraPatch	Excel Creatine Patch
ThermaCare Heatwraps	HoMedics Magnetic Therapy Patch
IcyHot Patch	Neutrogena On-the-Spot Acne Patch
Excedrin Cooling Patches	SunSpots Patches
TheraPatch Cold Sore	Curad Scar Therapy Patches
TheraPatch Psoriasis	Dr. Scholl s Clear Away Wart Removal
TheraPatch Vapor Kids	Nicotine Patches (various brands)
TheraPatch Anti-Itch	Crest Whitestrips

* The list is not all-inclusive
Source: Internet, retail stores.

incorporating drug delivery technology, with almost half of the research spending being dedicated to oral drug delivery.[2]

Transdermals Today and New Market Opportunities

Interest in transdermals has increased on several fronts over the last several years. Technology companies have generated additional clinical data demonstrating the potential of advanced transdermal technology. Pharmaceutical companies have become more aggressive in exploring alternate formulations to extend patent life, and several over-the-counter transdermal products have increased consumer awareness, acceptance and education on the benefit these systems have to offer.

Improved Technology

Transdermal Technology

Improvement in physical and chemical permeation enhancement technologies has led to renewed interest in transdermal drug delivery. Efforts from research work initiated in the late 1990s to increase skin permeation are beginning to emerge. Various academic and industrial laboratories have explored iontophoresis, electroporation, ultrasound and micro-poration using electrical current/voltage, radio frequency and microneedles to open up the skin.

Products using iontophoresis have already reached the US market. One example is Iomed's Iontocaine (Numby Stuff® – lidocaine HCl and epinephrine in the Phoresor iontophoresis system), which is marketed for local dermal analgesia. Similarly, Vyteris is awaiting approval for its iontophoretic system, which also delivers lidocaine for dermal anaesthesia in children. Several other companies have completed various stages of clinical studies on iontophoresis, most notable among them being ALZA with its E-TRANS® system using fentanyl for the management of post-operative pain.

Companies such as Altea Therapeutics, Transpharma and ALZA are using various microporation technologies to deliver peptides and proteins, vaccines and various pain medications transdermally. Initial clinical results are encouraging and have helped to bring greater attention to the potential of active transdermal technology. Clinical development continues in systems utilising electro-poration, sonophoresis and electronic component integrated technologies.

These new approaches to skin permeation will provide a means to deliver drugs that were previously difficult to pass through the highly impermeable skin barrier. Drugs with high molecular weights and drugs with blood levels that can be moderated electronically to give not only continuous pulsed doses, but drug on demand, are now being tested in clinical studies. Thus, the number of drug candidates is increasing for

2. *The Pharmaceutical R&D Compendium, CMR International.*

transdermal delivery and will cover drugs from pharmaceutical and biotechnology companies and new chemical entities that already exist today.

New Materials, Components and Product Designs

New Materials

New polymer adhesives have become available to advance transdermal technology. The polymers have been modified to improve solubility and drug diffusion with little change in adhesive and cohesive properties (3M's Latitude™). A hydrophilic pressure-sensitive adhesive (CORPLEX™) has been developed recently that has a versatile range of properties for water sorption and adhesion to moist skin and mucosa.[3]

New Transdermal Components and Product Designs

Corium has also been developing new designs of dermal and mucosal platforms to improve wear, skin permeation and ease of site application. Much of these product improvements have been possible through new and proprietary processes of Web handling, new ways of integrating various materials and the advent of mechanical and electronic interfaces with TDS. Not only have new materials allowed for improved wear properties, but the design of how adhesives are segregated from one another on one or more layers of film that also interface with skin or mucosa is enhancing wear properties. Noven has developed a technology that allows micro zones of two different types of adhesives to improve adhesion and drug release to achieve more hard-wearing and smaller patches than seen previously. Corium has developed some high-speed manufacturing processes that are allowing new ways to integrate film designs to improve wear properties and skin permeation.

Products have been designed that utilise microporation and other electronic means to vastly improve skin permeation, allowing them to be used as a diagnostic product. An example of a device/transdermal-like product that functions as a diagnostic product is the GlucoWatch – developed by Cygnus and distributed by Sankyo Pharmaceuticals. An auto sensor comprising hydrogel/enzyme films encased in hard plastic with metal electrodes, microchip and biosensor components is able to collect glucose levels via interstitial fluid This process of 'reverse' transdermal technology earns the distinction of being the first non-invasive product to address the need for invasive needle sticks to measure insulin levels.

The various methods of microporation of skin has created a whole new approach to achieving therapeutic blood levels that are superior or equivalent to those now under development in oral and inhalation delivery systems. Altea Therapeutics recently reported the results of delivery of insulin using their microporation technique (see *Figure 1*).[4] Another concept that has been successful in the consumer product arena is Proctor & Gamble's Crest Whitestrips™ – 'strips' of film that adhere to teeth and deliver hydrogen peroxide for whitening. Whitestrips™ and other products such as Listerine's PocketPak™ Films and Wrigley's Eclipse Film, which delivery a breath freshener and/or antibacterial agent, have reached exceptionally high acceptability in the marketplace. Annual sales exceeding several hundred million dollars demonstrate the speed with which consumers will embrace new technology in innovative markets.

Business Necessity Requires Renewed Exploration in Alternative Drug Formulations

Blockbuster Drugs Need Market Protection

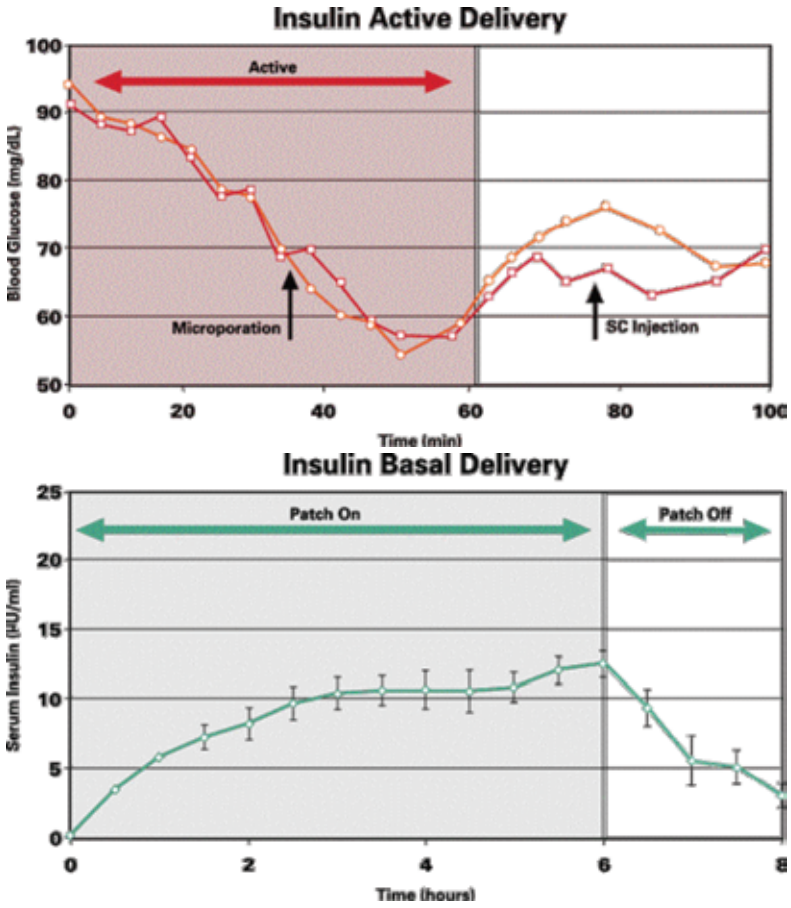
Reformulation of a product through the addition of a novel drug delivery system is a highly effective method to prolong a drug's revenue-generating life and provide new competitive advantages that may sustain or increase sales or halt a decline in market sales. Loss of a blockbuster drug due to patent expiration can be devastating to a product's sales. For example, sales of Bristol-Myers Squibb's Capoten® (captopril) fell 83% – from US$146 million to US$25 million – in the 12 months following its 1996 patent expiration. Merck's Vasotec® (enalapril) lost more than 80% of it market share within three months of patent expiration. Perhaps the most dramatic example was in 2001 when more than 65% of Eli Lilly's Prozac® sales were converted to generic sales in the first month after patent expiration.[5] *Table 3* outlines the 2001 sales of blockbuster drugs slated to expire from 2001 to 2010.[6]

Cost of Developing Patch/Generic Drugs Compared with New Chemical Entities

According to a study conducted by the Boston Consulting Group, the average cost of developing a drug is approximately US$500 million and can take as long as 15 years. On the other hand, transdermal development of known drugs can be significantly shorter and less expensive. It can take anything from four to eight years to develop a transdermal, at an

3. *Gary Cleary, et al., "CORPLEX™: Adhesive Hydrogels for Dermal and Mucosal Applications", abstract #123, 30th Annual Meeting and Exposition of the Controlled Release Society, Glasgow, Scotland, UK, 19–23 July 2003.*

Figure 1: Insulin Delivery Utilising Altea Therapeutics Microporation Delivery System



Source: http://www.alteatherapeutics.com

estimated cost of US$10–15 million. In addition, with investment under US$1 million, it is possible to determine the feasibility (*in vitro* and pilot human pharmacokinetics studies) of a drug within 12 months. Successful development of a novel formulation can extend a patent by as much as five years or longer if other barriers to entering the market arise. Conversion to a transdermal platform is clearly less expensive to develop than a newly discovered drug.

Specialty Pharmaceutical Companies

'Specialty pharmaceutical' companies (Watson, Shire and Barr) that have their roots in the generic drug business are also developing transdermals to differentiate themselves from the pure generic drug companies. This phenomenon has emerged over the last several years. These specialty companies are focusing on delivery platforms using newly or nearly expired drugs. As these various business strategies play out, there is more demand not only for transdermal technology, but for even more advanced transdermal technology.

Acceptance of Transdermal Platforms

There has been renewed interest lately by ethical and consumer pharmaceutical companies in transdermal technology. A large number of drug candidates for transdermal delivery have evolved, along with greater acceptance of transdermal delivery. Changes in the pharmaceutical environment have provided an increased opportunity for market acceptance.

In the late 1990s, nicotine transdermal products became available to the public over the counter and without a prescription. This exposure to the general populace, followed by the successful introduction of several over-the-counter/consumer patch-like products like Crest Whitestrips™ (see *Table 2*),[7] has begun to give the transdermal/dermal delivery platform popular acceptance and a place among other dosage forms in prescription, over-the-counter and consumer products and cosmeceutical products.

Opportunities in the Future

Transdermal drug delivery and patch-like delivery platforms and systems have had a rich past and are now emerging as a major alternative to other delivery platforms. As this platform has matured and new elements have been incorporated into its system, new products and applications in diagnostic and medical devices have shown new ways in which the skin and mucosa can play a larger part in healthcare and quality of life. This article has attempted to identify the various markets that are available, expanding to drugs with a larger molecular weight and further incorporation of 21st century technology into delivery systems.

Expansion of Patch Platforms to Various Markets

The platform itself has been widely accepted by the public in the US. There are many transdermal-like platforms found in prescription, over-the-counter, personal care and cosmeceutical products. These platforms extend across many therapeutic areas and are now not only putting drugs into the systemic circulation, but also locally into the skin or just below it (for example Triaminic® Cough and Cold Patch, which delivers product locally). In addition, these platforms have expanded market opportunities and now include the ability to withdraw biological markers from the skin as a diagnostic device (for example GlucoWatch®) and apply cosmetic to the teeth (for example Crest Whitestrips®), oral cavity (DentiPatch®) and other mucosal cavities including anal and vaginal.

4. *http://www.alteatherapeutics.com*
5. *IMS.*
6. *Decision Resources, June 2002.*

Table 3: Patent Expiration and Vulnerability of Blockbuster Drug Sales

Blockbuster Drug Patent Expirations, 2001-2010

Patent Expiration Year	Brand Name	Generic Name	Primary Indications	Company	Estimated U.S. Sales 2001 ($ MM)
2001	Taxol	Paclitaxel	Cancers	Bristol-Myers Squibb	545
	Allegra	Fexofenadine	Allergic rhinitis	Aventis	1,325
	Glucophage	Metformin	Type 2 diabetes	Bristol-Myers Squibb	2,024
	Prozac	Fluoxetine	Depression	Eli Lilly	1,659
	Prilosec	Omeprazole	Duodenal ulcers	AstraZeneca	3,999
	Lovenox	Enoxaparin	Prevention of deep vein thrombosis	Aventis	862
	Neurontin	Gabapentin	Partial seizures	Pfizer	1,510
	Levaquin	Levofloxacin	Bacterial infections	Johnson & Johnson	993
2002	Ultram	Tramadol	Analgesia	Johnson & Johnson	597
	Intron A	Pegylated interferon	Viral infections, cancers	Schering-Plough	750
	Zestril	Lisinopril	Hypertension	AstraZeneca	911
	Claritin	Loratadine	Allergic rhinitis	Schering-Plough	2,716
	Augmentin	Amoxicillin plus clavulanic acid	Bacterial infections	GlaxoSmithKline	1,313
2003	Cipro	Ciprofloxacin	Bacterial infections	Bayer	1,066
	Flovent	Fluticasone	Dermatoses	GlaxoSmithKline	677
	Singulair	Montelukast	Asthma	Merck & Co.	1,060
	Biaxin	Clarithromycin	Microbial infections	Abbott Laboratories	537
	Flonase	Fluticasone	Allergic rhinitis	GlaxoSmithKline	539
	Ortho-Tri-Cyclen	Norgestimate/ ethinyl estradiol	Contraception	Johnson & Johnson	768
	Avonex	Beta interferon	Multiple sclerosis	Biogen	709
2004	Diflucan	Fluconazole	Fungal infections	Pfizer	576
	Epogen	Erythropoietin	Anemia	Amgen	1,937
	Procrit (Epoetin)	Erythropoietin	Anemia	Johnson & Johnson	2,335
2005	Prevacid	Lansoprazole	Duodenal ulcers	TAP Pharmaceuticals	2,951
	Zocor	Simvastatin	Hyperlipidemia	Merck	4,690
	Zoloft	Sertraline	Depression	Pfizer	1,929
	Pravachol	Pravastatin	Hyperlipidemia	Bristol-Myers Squibb	1,366
	Lupron	Luprolide	Prostate cancer	TAP Pharmaceuticals	833
	Celexa	Citalopram	Depression	Forest Laboratories	1,140
2006	Ambien	Zolpidem	Insomnia	Pharmacia	896
	Paxil	Paroxetine	Depression	GlaxoSmithKline	1,803
	Norvasc	Amlodipine	Hypertension	Pfizer	1,667
	Zithromax	Azithromycin	Bacterial infections	Pfizer	1,137
	Imitrex	Sumatriptan	Migraine	GlaxoSmithKline	828
	Zofran	Ondansetron	Nausea, vomiting	GlaxoSmithKline	616
2007	Zyrtec	Cetirizine	Allergic rhinitis	Pfizer	990
	Fosamax	Alendronate	Osteoporosis	Merck & Co.	1,275
	Risperdal	Risperidone	Psychoses	Johnson & Johnson	1,240
	Effexor	Venlafaxine	Depression	Wyeth	1,098
2008	Neupogen	Filgrastim	Febrile neutropenia	Amgen	1,237
	Depakote	Divalproex	Bipolar disorder	Abbott Laboratories	869

Note: Table includes all products with patents expiring between 2001 and 2010 that achieved U.S. sales in excess of $500 million in 2001. No products with patents expiring in 2009 or 2010 achieved this level of sales in 2001.

Source: Decision Resources, June 2002.

Increase in Traditional Drugs and Drugs with Large Molecular Weight

We are close to the brink of the introduction of new systems that will enable drugs with a large molecular weight to pass through the skin. Platform designs and manufacturing processes that will advance wear properties, skin permeability, ease of application and production efficiency are making transdermal platforms extremely attractive. Because pharmaceutical companies still have preconceived notions of what the transdermal market has to offer, it is incumbent on the transdermal drug delivery technology companies to do a better job in educating ethical and consumer pharmaceutical companies on the advancements of the technology, the benefits of this technology and, equally importantly, physician and consumer acceptance of the technology.

New Materials and Patch Platform Designs

As more and more polymers become available for use on skin, there will be more opportunities for platform designs to improve wear properties and diffusion of active molecules from the patch. This will lead to smaller patches and an increase in the number of drug candidates. Through integration of electronics and nanotechnology with patch-like platforms, new approaches to drug delivery, wound care and monitoring and diagnostic methods that utilise the skin or mucosa as a portal for delivery are enabling patch-like platforms to play an important role in healthcare to treat, measure, diagnose and generally improve quality of life. ■

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7. *Internet and retail store searches, 2003.*